REMARKS

Claims 39-43, and 46-67 constitute the pending claims in the present application. Applicants have cancelled claims 1-28, 44 and 45. The cancellations have been made solely to expedite prosecution. Applicants reserve the right to pursue claims of similar or differing scope to the cancelled claims at a later time. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action. Applicants respectfully request reconsideration in view of the following remarks.

1. Applicants have taken steps to conform with 37 CFR 1.121(b)(1)(iii) and (c)(1)(ii) as requested by the Examiner. Applicants have presented above marked-up copies of amendments on pages separate from the amendment.

2. Applicants have enclosed the declaration signed by Inventor Bachovchin with this Office Action.

3. Applicants have filed formal drawings including Figure 3 with this Office Action.

4. The claim for priority inserted by the preliminary amendment filed July 28, 2000, is objected to as not indicate what type of priority is being claimed. Applicants have amended the July 28 preliminary amendment, and have included a new Declaration with this Response. Thus, Applicants assert that there is proper co-pendency between the two applications. Applicants respectfully request reconsideration of the Examiner's objection.

5. Applicants have corrected misspelled words "halogentated" and "lik" in the specification at page 18, line 6 and line 9.

6. Claims 15-17, 19, 27, 42, 43, 54-56, 58-61 and 66 are objected to under 35 U.S.C. 112 1st paragraph, for containing subject matter which was not described in the specification. The Office Action stated that there was no original disclosure supporting the recitation that X_1 can be a hydroxyl as is recited in the instant claims 15, 16, 27, 54, 55 and 66. With respect to claims 15, 16, and 27, Applicants assert the objection has

been rendered moot in light of the cancellation. With respect to claims 54, 55, and 66 applicants have amended the claims by removing references to hydroxyl. These amendments have been entered solely to expedite prosecution. Applicants reserve the right to prosecute claims of similar or differing scope in the future. Additionally, with respect to claims 54, 55, and 66 removed references to hydrogen from the recitation of functional groups for X_1. The skilled artisan would have recognized that X_1 needs to be a halogen and not a hydrogen in order to make the functional groups X1 is attached to electrophilic. The Office Action further stated that there was no original disclosure of cause of the glucose intolerance cited in claim 42. Applicants have amended claim 42 to clarify that it the disruption stated in the claim is that of the GLP-1 receptor and not the GLP gene. Applicants direct the Examiner's attention to page 51 line 6 of the application where Applicants disclosed that knock-outs of GLP-1 receptor genes cause glucose intolerance. Applicants assert that there is no inconsistency with the cause of glucose intolerance recited in instant amended claim 42 and the proposed mechanism of Applicants invention. Accordingly Applicants respectfully request removal of the objection.

7. Claims 27, 31-36, and 47-67 are rejected under 35 U.S.C. 112 2nd paragraph, as being indefinite. Claims 27, 31, 65 and 66 were deemed indefinite because they defined variables which are not used in any of the chemical structures found in the claims. Applicants thank the Examiner for pointing out the extraneous variables, and have removed the recitation of these variables. Applicants assert that the removal of the variables in no way narrows the scope of these claims. Applicants respectfully request removal of the rejection.

Claim 27 was rejected under 35 U.S.C. 112 2nd paragraph, because the second structure is incomplete due to "the double bond between the –CH and the NR_5 groups has been replaced with a single bond." While the rejection has been rendered moot in light of cancellation of this claim. Applicants would, nevertheless, like to point out that they are unaware of any previous amendments changing the double bond to a single bond. Any such change is not reflected in the copies of Office Action responses within Applicants' possession. Applicants assert that in the last response a $–CH=NR_5$ group was added, and

the addition was duly noted in the marked-up copy. Accordingly, Applicants respectfully request removal of the rejection.

Claim 47-54 and 63-67 which depend on claim 41 were rejected under 35 U.S.C. 112 2nd paragraph, because there was no antecedent basis in claim 41 for the phrase "the inhibitor". Applicants have amended claim 41 to establish a proper antecedent basis. Accordingly, Applicants respectfully request removal of the rejection.

8. Claim 8, 16, 26, 28, 40, 42, 43 and 47-67 were objected to because of informalities. Applicants thank the Examiner for pointing out the informalities, and have made the necessary corrections. Thus, Applicants assert that these corrections in no way narrow the scope of these claims. Applicants respectfully request removal of the objection

Claims 22 and 61 were objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of claim 15 and 54 respectively upon which they depend. Applicants submit that the objection has been rendered moot with respect to claim 22. Claim 61 recite that R_5 can be a halogenated lower alkyl, which the Office Action states "is not a possibility embraced by the definition of R_5 in claim ... 54." Claim 54 defines R_5 to include an alkyl group. Applicants' specification defines an alkyl group or a lower alkyl group to include alkyls substituted with a halogen.(See Specification, page 19 ln 31) The specification states that have 30 or lower carbon atoms.(See Specification, page 19, lns 24-30) Lower alkyl is defined as an alkyl group but having from one to ten carbons, more preferably from one to six carbon atoms in its backbone structure.(See Specification, page 20 ln 15-17) As such, a skilled artisan would recognize that the use of the term "lower halogenated alkyl" further limits an alkyl group. Therefore, Applicants assert that there is proper dependence between the claims. Applicants respectfully request removal of the objection.

9. Claim 28 was objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit claim 15 upon which it depends. Specifically, the Office Action stated "the general formula recited in claim 28 does not comprise the 4-8 member

heterocycle required by claim 15." Applicants have cancelled these claims thereby rendering this rejection moot.

Claim 44 and 45 were objected to under 37 CFR 1.75(c), as being of improper dependent form for having an identical scope as claim 38 upon which they depend. Applicants have cancelled these claims thereby rendering this rejection moot.

Claims 51 and 67 were objected to under 37 CFR 1.75(c), as being of improper dependent form for having a broader scope than claim 41 upon which they depend. Applicants have severed the dependency between the claims. Accordingly, Applicants respectfully request removal of all objections made under 37 CFR 1.75(c).

11. Claims 1-3, 5-13, 15, 16, 20, 21, 25, and 29 are rejected under 35 U.S.C 102(b) as being anticipated by the WO Patent Application '309. Applicants submit that the rejection has been rendered moot because Applicants have cancelled the rejected claims.

12. Claims 1-3, 5-24, 26, 27, and 29-37 are rejected under 35 U.S.C 102(b) as being anticipated by the WO Patent Application '259. Applicants submit that the rejection has been rendered moot because Applicants have cancelled the rejected claims.

13-17. In points 13-17 the Office Action posed both 102 and 103 rejections based in part on the disclosure of Deacon et al. Applicants respectfully traverse these rejections. Applicants assert that the instant application is a continuation of the PCT Application US99/02294 filed on 02/02/99, which in turn claims priority to the US Application 60/073,409, filed on 02/02/98. Applicants have entered an amendment to the specification to establish the earlier priority date, proper copendency. Applicants assert that in the absence of Deacon et al. none of the 102 or 103 rejections in points 13-17 can stand. Accordingly, Applicants respectfully request reconsideration and removal of these rejection.

18 and 19. Claims 1-3, 5-13, 15-18, 20, 21, 24, 29-35, and 37 are rejected under 35 U.S.C. 102(b) as being anticipated by the WO Patent Application 98/25644 (hereafter

referred to as the '644 Application), and rejected under 35 U.S.C. 103(a) as being obvious over the same reference. Applicants submit that the rejection has been rendered moot because Applicants have cancelled the rejected claims.

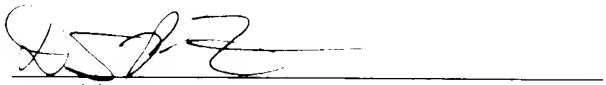
20. Claims 1-17, 20, 21, 29, 38, 39, 44-56, 59, and 60 are rejected under 35 U.S.C. 102(a) and (e) as being anticipated by Villhauer. Applicants submit that the rejection has been rendered moot with regards to claims 1-17, 20, 21, and 29 because Applicants have cancelled the rejected claims. For the remaining claims, claims 38, 39, 44-56, 59, and 60, Applicants respectfully traverse the rejection to the extent that it is maintained over the amendments entered. With respect to claims 38-39, 44-53, Applicants assert that Villhauer does not teach treating glucose intolerant animals. Thus Villhauer does not teach all the elements of the instant claims, and therefore fails to anticipate the claims. Applicants point out that the remaining claims, as amended, do not include compounds covered by Villhauer. All of Villhauer's compounds have a cyano group attached to a modified prolyl residue. The instant claims recite compounds wherein a cyano group is not listed among the substituents of the corresponding prolyl residue. Therefore, Applicants assert that an anticipation rejection cannot be sustained. Accordingly, Applicants respectfully request reconsideration and removal of the rejection.

21. Claims 1-14, 29, 38-40 and 44-52 are rejected under 35 U.S.C. 102(b) as being anticipated by German Patent 19616486 (hereinafter referred to as the '486 patent). Applicants submit that the rejection has been rendered moot with regards to claims 1-14, and 29 because Applicants have cancelled the rejected claims. For the remaining claims, 38-40, and 44-52, Applicants traverse the rejection to the extent that it is maintained over the amendments entered. The instant claims, as amended, are directed to uses of DPIV inhibitors to modify GLP-1 metabolism in a glucose intolerant animal. Applicants assert that the '486 patent neither discloses compounds within the scope of instant claims, nor does it teach modifying GLP-1 metabolism in a glucose intolerant animal. Thus the '486 patent does not disclose every limitation of the pending claims, and therefore does not anticipate the claims. Accordingly, Applicants respectfully request reconsideration and removal of the rejection.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945.**

Respectfully Submitted,



Date: July 18, 2002

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In the specification:

Please replace paragraph at page 18, line 6, with:

In preferred embodiments, R5 is a hydrogen, or a halogenated lower alkyl.

Please replace paragraph at page 18, line 9, with:

In preferred embodiments, R_{61} and R_{62}, independently, represent lower alkyls, such as methyl, ethyl, propyl, isopropyl, tert-butyl or the like;

The paragraphs presented above incorporates changes as indicated by the marked-up version below.

Page 18, line 6:

In preferred embodiments, R5 is a hydrogen, or a ~~halogentated~~ halogenated lower alkyl.

Page 18, line 9:

In preferred embodiments, R_{61} and R_{62}, independently, represent lower alkyls, such as methyl, ethyl, propyl, isopropyl, tert-butyl or the ~~lik.~~ like;

The claims presented above incorporate changes as indicated by the marked-up versions below.

38. (Amended) A method for modifying glucose metabolism in a glucose intolerant animal, comprising administering to the animal a composition including one or more protease inhibitors which inhibit DPIV-mediated proteolysis with a Ki in the nanomolar or less range.

39. (Amended) A method for modifying glucose metabolism in a glucose intolerant animal, comprising administering to the animal a composition including one or more protease inhibitors which inhibit the proteolysis of glucagon-like peptide 1 (GLP-1) with a Ki in the nanomolar or less range.

40. (Amended) A method for modifying~~, in a glucose intolerant animal,~~ metabolism of a peptide hormone in a glucose intolerant animal, comprising administering to the animal a composition including one or more inhibitors of dipeptidylpeptidase IV (DPIV), wherein the inhibitor inhibits DPIV with a K_i in the nanomolar or less range, ~~with~~ in an amount sufficient to increase the plasma half-life of the peptide hormone, which peptide hormone is selected from glucagon-like peptide 2 (GLP-2), growth hormone-releasing factor (GHRF), vasoactive intestinal peptide (VIP), peptide histidine isoleucine (PHI), pituitary adenylate cyclase activating peptide (PACAP), gastric inhibitory peptide (GIP), helodermin, Peptide YY and neuropeptide Y.

41. (Amended) A method for modifying glucose metabolism of a glucose intolerant animal, comprising administering to the animal a composition including a boronyl peptidomimetic inhibitor of a peptide selected from Pro-Pro, Ala-Pro, and (D)-Ala-(L)-Ala.

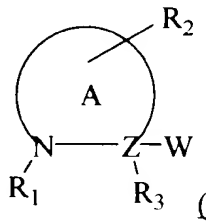
42. (Amended) The method of ~~any of claims 38-41~~ claim 41 wherein, the glucose intolerance in the animal is a result of a deletion or disruption of the gene encoding for a glucagon type peptide 1 (GLP-1) receptor.

46. (Amended) The method of claim 38 ~~or~~, 39, 40 or 41 wherein administering the inhibitor reduces one or more of insulin resistance, glucose intolerance, hyperglycemia, hyperinsulinemia, obesity, hyperlipidemia, or hyperlipoproteinemia.

48. (Amended) The method of claim 38, 39, 40 or 41, wherein the inhibitor has an EC_{50} for inhibition of glucose tolerance in the nanomolar or less range.

51. (Amended) The method of claim 38, 39, or 40, ~~or 41,~~ wherein the inhibitor is peptidomimetic of a peptide selected from Pro-Pro, Ala-Pro, and (D)-Ala-(L)-Ala.

54. (Amended) The method of claim 38, 39, 40, or 41, wherein the inhibitor is represented by the general Formula VII:



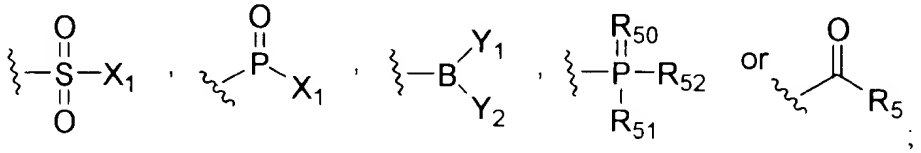
(VII)

wherein,

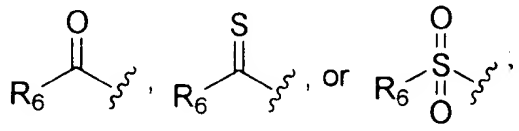
A represents a 4-8 membered heterocycle including a N and a Cα carbon;

Z represents C or N;

W represents ~~-CN, -CH=NR5~~,



R_1 represents a C-terminally linked amino acid residue or amino acid analog, or a C-terminally linked peptide or peptide analog, or an amino-protecting group,



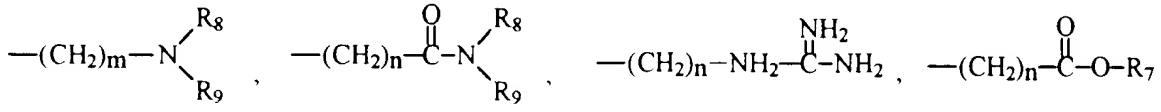
R_2 is absent or represents one or more substitutions to the ring A, each of which can independently be a halogen, a lower alkyl, a lower alkenyl, a lower alkynyl, a carbonyl, a thiocarbonyl, an amino, an acylamino, an amido, a cyano, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, $-(CH_2)_m-R_7$, $-(CH_2)_m-OH$, $-(CH_2)_m-O$-lower alkyl, $-(CH_2)_m-O$-lower alkenyl, $-(CH_2)_n-O-(CH_2)_m-R_7$, $-(CH_2)_m-SH$, $-(CH_2)_m-S$-lower alkyl, $-(CH_2)_m-S$-lower alkenyl, or $-(CH_2)_n-S-(CH_2)_m-R_7$;

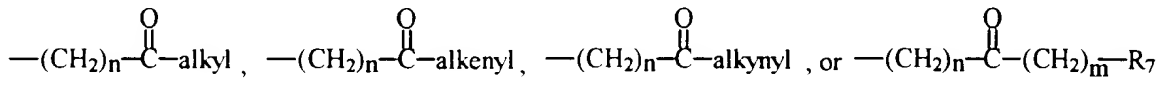
if Z is N, R_3 represents a hydrogen;

if Z is C, R_3 represents a hydrogen or a halogen, a lower alkyl, a lower alkenyl, a lower alkynyl, a carbonyl, a thiocarbonyl, an amino, an acylamino, an amido, a cyano, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, $-(CH_2)_m-R_7$, $-(CH_2)_m-OH$, $-(CH_2)_m-O$-lower alkyl, $-(CH_2)_m-O$-lower alkenyl, $-(CH_2)_n-O-(CH_2)_m-R_7$, $-(CH_2)_m-SH$, $-(CH_2)_m-S$-lower alkyl, $-(CH_2)_m-S$-lower alkenyl, or $-(CH_2)_n-S-(CH_2)_m-R_7$;

R_5 represents a hydrogen, an alkyl, an alkenyl, an alkynyl, $-C(X_1)(X_2)X_3$, $-(CH_2)_m-R_7$, $-(CH_2)_n-OH$, $-(CH_2)_n-O$-alkyl, $-(CH_2)_n-O$-alkenyl, $-(CH_2)_n-O$-alkynyl, $-(CH_2)_n-O-(CH_2)_m-R_7$, $-(CH_2)_n-SH$, $-(CH_2)_n-S$-alkyl, $-(CH_2)_n-S$-alkenyl, $-(CH_2)_n-S$-alkynyl, $-(CH_2)_n-S-(CH_2)_m-R_7$, $-C(O)C(O)NH_2$, or $-C(O)C(O)OR'_7$;

R_6 represents a hydrogen, a halogen, an alkyl, an alkenyl, an alkynyl, an aryl, $-(CH_2)_m-R_7$, $-(CH_2)_m-OH$, $-(CH_2)_m-O$-alkyl, $-(CH_2)_m-O$-alkenyl, $-(CH_2)_m-O$-alkynyl, $-(CH_2)_m-O-(CH_2)_m-R_7$, $-(CH_2)_m-SH$, $-(CH_2)_m-S$-alkyl, $-(CH_2)_m-S$-alkenyl, $-(CH_2)_m-S$-alkynyl, $-(CH_2)_m-S-(CH_2)_m-R_7$,





R_7 represents, for each occurrence, a substituted or unsubstituted aryl, aralkyl, cycloalkyl, cycloalkenyl or heterocyclyl;

R'_7 represents, for each occurrence, hydrogen, or a substituted or unsubstituted alkyl, alkenyl, aryl, aralkyl, cycloalkyl, cycloalkenyl or heterocyclyl;

R_8 and R_9 each independently represent hydrogen, alkyl, alkenyl, $-(CH_2)_m-R_7$, -C(=O)-alkyl, -C(=O)-alkenyl, -C(=O)-alkynyl, or $-C(=O)-(CH_2)_m-R_7$,

or R_8 and R_9 taken together with the N atom to which they are attached complete a heterocyclic ring having from 4 to 8 atoms in the ring structure;

R_{50} represents O or S;

R_{51} represents N_3, SH, NH_2, NO_2 or OR'_7;

R_{52} represents hydrogen, a lower alkyl, an amine, OR'_7, or a pharmaceutically acceptable salt, or R_{51} and R_{52} taken together with the phosphorous atom to which they are attached complete a heterocyclic ring having from 5 to 8 atoms in the ring structure;

X_1 represents ~~a hydrogen or~~ a halogen~~, or a hydroxyl~~;

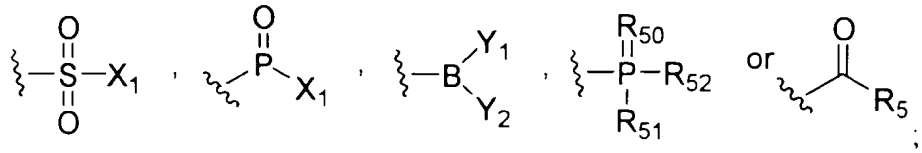
X_2 and X_3 each represent a hydrogen or a halogen;

m is zero or an integer in the range of 1 to 8; and

n is an integer in the range of 1 to 8.

55. (Amended) The method of claim 54, wherein;

W represents ~~-CN,~~ -CH=NR$_5$,



R$_5$ represents a hydrogen, an alkyl, an alkenyl, an alkynyl, -C(X$_1$)(X$_2$)X$_3$, -(CH$_2$)$_m$-R$_7$, -(CH$_2$)$_n$-OH, -(CH$_2$)$_n$-O-alkyl, -(CH$_2$)$_n$-O-alkenyl, -(CH$_2$)$_n$-O-alkynyl, -(CH$_2$)$_n$-O-(CH$_2$)$_m$-R$_7$, -(CH$_2$)$_n$-SH, -(CH$_2$)$_n$-S-alkyl, -(CH$_2$)$_n$-S-alkenyl, -(CH$_2$)$_n$-S-alkynyl, -(CH$_2$)$_n$-S-(CH$_2$)$_m$-R$_7$, -C(O)C(O)NH$_2$, or -C(O)C(O)OR'$_7$;

R$_7$ represents, for each occurrence, a substituted or unsubstituted aryl, aralkyl, cycloalkyl, cycloalkenyl or heterocyclyl;

R'$_7$ represents, for each occurrence, hydrogen, or a substituted or unsubstituted alkyl, alkenyl, aryl, aralkyl, cycloalkyl, cycloalkenyl or heterocyclyl;

Y$_1$ and Y$_2$ can independently or together be hydroxyl, or taken together Y$_1$ and Y$_2$ are connected via a ring having from 5 to 8 atoms in the ring structure which is hydrolyzed to hydroxy groups under physiological conditions;

R$_{50}$ represents O or S;

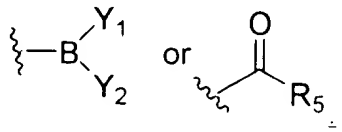
R$_{51}$ represents N$_3$, SH, NH$_2$, NO$_2$ or OR'$_7$;

R$_{52}$ represents hydrogen, a lower alkyl, an amine, OR'$_7$, or a pharmaceutically acceptable salt, or R$_{51}$ and R$_{52}$ taken together with the phosphorous atom to which they are attached complete a heterocyclic ring having from 5 to 8 atoms in the ring structure;

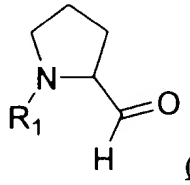
X_1 represents ~~a hydrogen or~~ a halogen~~, or a hydroxyl~~; and

X_2 and X_3 each represent a hydrogen or a halogen.

57. (Amended) The method of claim 54, wherein W represents



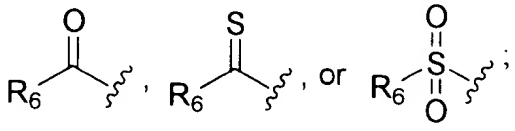
64. (Amended) The method of claim 54, wherein the inhibitor is represented by the general Formula IX:



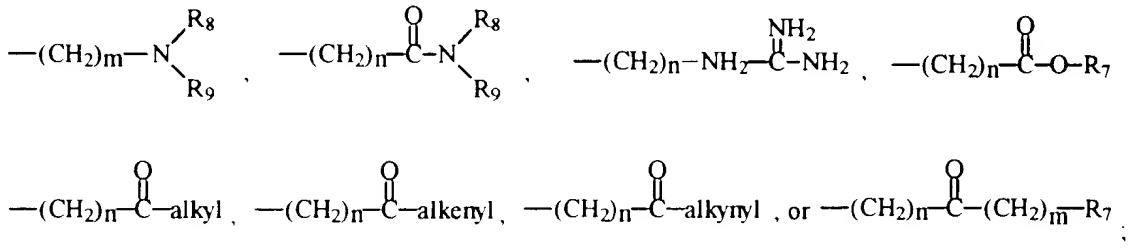
(IX)

wherein

R_1 represents a C-terminally linked amino acid residue or amino acid analog, or a C-terminally linked peptide or peptide analog,



R_6 represents a hydrogen, a halogen, an alkyl, an alkenyl, an alkynyl, an aryl, $-(CH_2)_m-R_7$, $-(CH_2)_m-OH$, $-(CH_2)_m-O-alkyl$, $-(CH_2)_m-O-alkenyl$, $-(CH_2)_m-O-alkynyl$, $-(CH_2)_m-O-(CH_2)_m-R_7$, $-(CH_2)_m-SH$, $-(CH_2)_m-S-alkyl$, $-(CH_2)_m-S-alkenyl$, $-(CH_2)_m-S-alkynyl$, $-(CH_2)_m-S-(CH_2)_m-R_7$,



R_7 represents an aryl, a cycloalkyl, a cycloalkenyl, or a heterocycle;

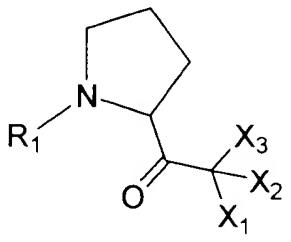
R_8 and R_9 each independently represent hydrogen, alkyl, alkenyl, $-(CH_2)_m-R_7$, -C(=O)-alkyl, -C(=O)-alkenyl, -C(=O)-alkynyl, or $-C(=O)-(CH_2)_m-R_7$,

or R_8 and R_9 taken together with the N atom to which they are attached complete a heterocyclic ring having from 4 to 8 atoms in the ring structure;

m is zero or an integer in the range of 1 to 8; and

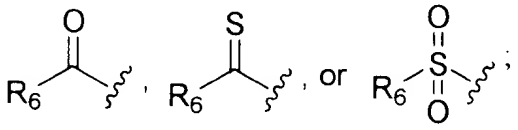
n is an integer in the range of 1 to 8.

65. (Amended) The method of claim 54, wherein the inhibitor is represented by the general formula:



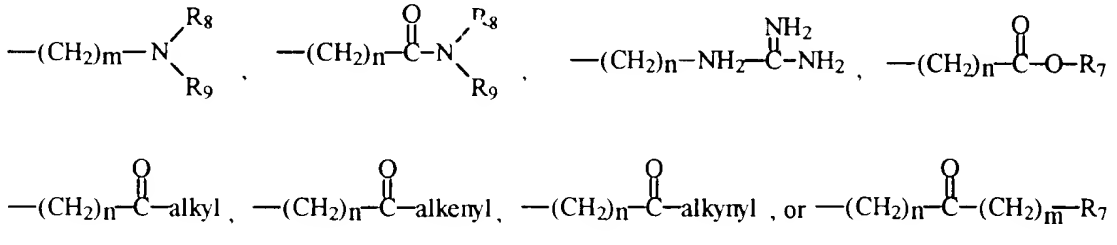
wherein,

R_1 represents a C-terminally linked amino acid residue or amino acid analog, or a C-terminally linked peptide or peptide analog,



~~R_4 represents a small hydrophobic group;~~

R_6 represents a hydrogen, a halogen, an alkyl, an alkenyl, an alkynyl, an aryl, $-(CH_2)_m-R_7$, $-(CH_2)_m-OH$, $-(CH_2)_m-O-alkyl$, $-(CH_2)_m-O-alkenyl$, $-(CH_2)_m-O-alkynyl$, $-(CH_2)_m-O-(CH_2)_m-R_7$, $-(CH_2)_m-SH$, $-(CH_2)_m-S-alkyl$, $-(CH_2)_m-S-alkenyl$, $-(CH_2)_m-S-alkynyl$, $-(CH_2)_m-S-(CH_2)_m-R_7$,



R_7 represents an aryl, a cycloalkyl, a cycloalkenyl, or a heterocycle;

R_8 and R_9 each independently represent hydrogen, alkyl, alkenyl, $-(CH_2)_m-R_7$, $-C(=O)-alkyl$, $-C(=O)-alkenyl$, $-C(=O)-alkynyl$, $-C(=O)-(CH_2)_m-R_7$,

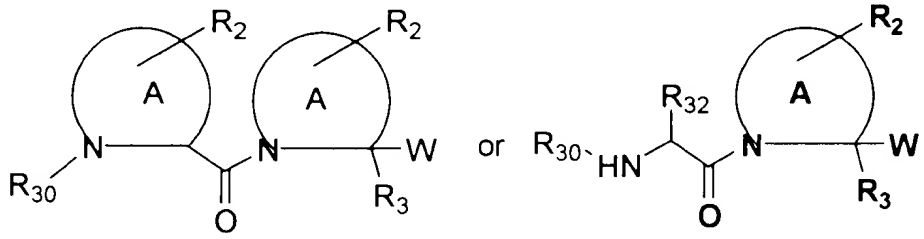
or R_8 and R_9 taken together with the N atom to which they are attached complete a heterocyclic ring having from 4 to 8 atoms in the ring structure;

X_1, X_2 and X_3 each represent a hydrogen or a halogen; ~~and~~

m is zero or an integer in the range of 1 to 8; and

n is an integer in the range of 1 to 8.

66. (Amended) The method of claim 54, wherein the inhibitor is represented by the general Formulae Xa or Xb:

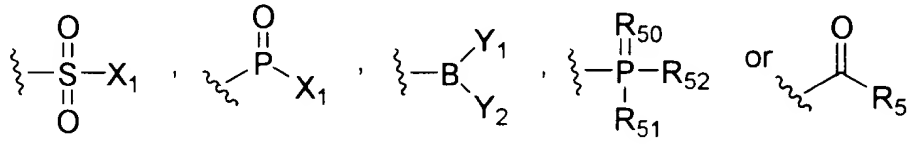


(Xa) **(Xb)**

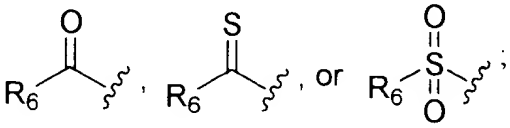
wherein,

A represents a 4-8 membered heterocycle including a N and a Cα carbon;

W represents ~~-CN,~~ -CH=NR$_5$,



R_1 represents a C-terminally linked amino acid residue or amino acid analog, or a C-terminally linked peptide or peptide analog, or an amino-protecting group,



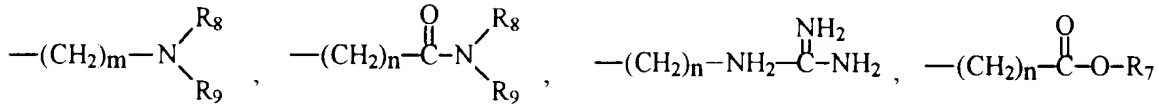
;

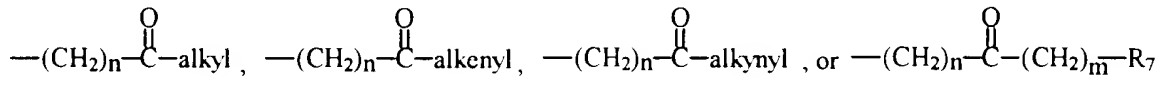
R_3 represents a hydrogen or a halogen, a lower alkyl, a lower alkenyl, a lower alkynyl, a carbonyl, a thiocarbonyl, an amino, an acylamino, an amido, a cyano, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, -$(CH_2)_m$-R_7, -$(CH_2)_m$-OH, -$(CH_2)_m$-O-lower alkyl, -$(CH_2)_m$-O-lower alkenyl, -$(CH_2)_n$-O-$(CH_2)_m$-R_7, -$(CH_2)_m$-SH, -$(CH_2)_m$-S-lower alkyl, -$(CH_2)_m$-S-lower alkenyl, or -$(CH_2)_n$-S-$(CH_2)_m$-R_7;

R_5 represents a hydrogen, an alkyl, an alkenyl, an alkynyl, -$C(X_1)(X_2)X_3$, -$(CH_2)_m$-R_7, -$(CH_2)_n$-OH, -$(CH_2)_n$-O-alkyl, -$(CH_2)_n$-O-alkenyl, -$(CH_2)_n$-O-alkynyl, -$(CH_2)_n$-O-

$(CH_2)_m$-R_7, -$(CH_2)_n$-SH, -$(CH_2)_n$-S-alkyl, -$(CH_2)_n$-S-alkenyl, -$(CH_2)_n$-S-alkynyl, -$(CH_2)_n$-S-$(CH_2)_m$-R_7, -C(O)C(O)NH_2, or -C(O)C(O)OR'$_7$;

R_6 represents a hydrogen, a halogen, an alkyl, an alkenyl, an alkynyl, an aryl, -$(CH_2)_m$-R_7, -$(CH_2)_m$-OH, -$(CH_2)_m$-O-alkyl, -$(CH_2)_m$-O-alkenyl, -$(CH_2)_m$-O-alkynyl, -$(CH_2)_m$-O-$(CH_2)_m$-R_7, -$(CH_2)_m$-SH, -$(CH_2)_m$-S-alkyl, -$(CH_2)_m$-S-alkenyl, -$(CH_2)_m$-S-alkynyl, -$(CH_2)_m$-S-$(CH_2)_m$-R_7,





R_7 represents, for each occurrence, a substituted or unsubstituted aryl, aralkyl, cycloalkyl, cycloalkenyl or heterocyclyl;

R'$_7$ represents, for each occurrence, hydrogen, or a substituted or unsubstituted alkyl, alkenyl, aryl, aralkyl, cycloalkyl, cycloalkenyl or heterocyclyl;

R_8 and R_9 each independently represent hydrogen, alkyl, alkenyl, -$(CH_2)_m$-R_7, -C(=O)-alkyl, -C(=O)-alkenyl, -C(=O)-alkynyl, or -C(=O)-$(CH_2)_m$-R_7,

or R_8 and R_9 taken together with the N atom to which they are attached complete a heterocyclic ring having from 4 to 8 atoms in the ring structure;

R_{32} is a small hydrophobic group;

R_{30} represents a C-terminally linked amino acid residue or amino acid analog, or a C-terminally linked peptide or peptide analog, or an amino-protecting group;

R_{50} represents O or S;

R_{51} represents N_3, SH, NH_2, NO_2 or OR'_7;

R_{52} represents hydrogen, a lower alkyl, an amine, OR'_7, or a pharmaceutically acceptable salt, or R_{51} and R_{52} taken together with the phosphorous atom to which they are attached complete a heterocyclic ring having from 5 to 8 atoms in the ring structure;

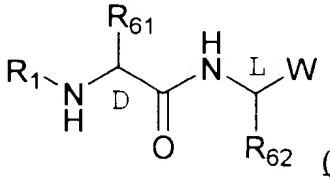
X_1 represents ~~a hydrogen or~~ a halogen~~, or a hydroxyl~~;

X_2 and X_3 each represent a hydrogen or a halogen;

m is zero or an integer in the range of 1 to 8; and

n is an integer in the range of 1 to 8.

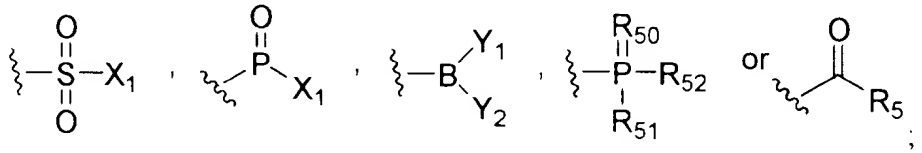
67. (Amended) The method of claim 38, 39, or 40, ~~or 41,~~ wherein the inhibitor is represented by the general Formula XI:



(XI)

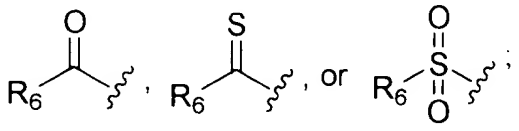
wherein,

W represents a functional group which reacts with an active site residue of the targeted protease selected from -CN, -CH=NR_5,



;

R_1 represents a C-terminally linked amino acid residue or amino acid analog, or a C-terminally linked peptide or peptide analog, or an amino-protecting group, or



R_3 represents hydrogen or a halogen, a lower alkyl, a lower alkenyl, a lower alkynyl, a carbonyl, a thiocarbonyl, an amino, an acylamino, an amido, a cyano, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, $-(CH_2)_m-R_7$, $-(CH_2)_m-OH$, $-(CH_2)_m-O$-lower alkyl, $-(CH_2)_m-O$-lower alkenyl, $-(CH_2)_n-O-(CH_2)_m-R_7$, $-(CH_2)_m-SH$, $-(CH_2)_m-S$-lower alkyl, $-(CH_2)_m-S$-lower alkenyl, or $-(CH_2)_n-S-(CH_2)_m-R_7$;

R_5 represents H, an alkyl, an alkenyl, an alkynyl, $-C(X_1)(X_2)X_3$, -(CH2)m-R_7, -(CH2)n-OH, -(CH2)n-O-alkyl, -(CH2)n-O-alkenyl, -(CH2)n-O-alkynyl, -(CH2)n-O-(CH2)m-R_7, -(CH2)n-SH, -(CH2)n-S-alkyl, -(CH2)n-S-alkenyl, -(CH2)n-S-alkynyl, -(CH2)n-S-(CH2)m-R_7, $-C(O)C(O)NH_2$, or $-C(O)C(O)OR'_7$;

R_6 represents a hydrogen, a halogen, an alkyl, an alkenyl, an alkynyl, an aryl, $-(CH_2)_m-R_7$, $-(CH_2)_m-OH$, $-(CH_2)_m-O$-alkyl, $-(CH_2)_m-O$-alkenyl, $-(CH_2)_m-O$-alkynyl, $-(CH_2)_m-O-(CH_2)_m-R_7$, $-(CH_2)_m-SH$, $-(CH_2)_m-S$-alkyl, $-(CH_2)_m-S$-alkenyl, $-(CH_2)_m-S$-alkynyl, or $-(CH_2)_m-S-(CH_2)_m-R_7$;

R_7 represents, for each occurrence, a substituted or unsubstituted aryl, aralkyl, cycloalkyl, cycloalkenyl or heterocyclyl;

R'_7 represents, for each occurrence, hydrogen, or a substituted or unsubstituted alkyl, alkenyl, aryl, aralkyl, cycloalkyl, cycloalkenyl or heterocyclyl;

R_{61} and R_{62}, independently, represent small hydrophobic groups;

Y_1 and Y_2 can independently or together be OH or an alkoxyl, or taken together Y_1 and Y_2 are connected via a ring having from 5 to 8 atoms in the ring structure which is hydrolyzed to hydroxy groups under physiological conditions;

R_{50} represents O or S;

R_{51} represents N_3, SH, NH_2, NO_2 or OR'_7;

R_{52} represents hydrogen, a lower alkyl, an amine, OR'_7, or a pharmaceutically acceptable salt, or R_{51} and R_{52} taken together with the phosphorous atom to which they are attached complete a heterocyclic ring having from 5 to 8 atoms in the ring structure;

X_1 represents a halogen;

X_2 and X_3, independently for each occurrence, represent a hydrogen or a halogen;

m is zero or an integer in the range of 1 to 8; and

n is an integer in the range of 1 to 8.